

APPENDIX B
Version with Markings to Show Changes Made
37 C.F.R. § 1.121(b)(iii) and (c)(ii)

SPECIFICATION:

Paragraph at page 3, lines 11-15:

The present invention also provides a liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 10 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween] TWEEN[®] 80.

Paragraph at page 3, lines 16-20:

The present invention further provides a liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween] TWEEN[®] 80.

Paragraph at page 12, line 24 to page 13, line 15:

Example 1

The following study examines the effect of the concentration of citric acid on the bioavailability and plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as described previously 20µl of rsCT (200µg/ml) in 0.85% sodium chloride, 0.1% [Tween] TWEEN[®] 80, 0.2% phenylethyl alcohol, 0.5% benzyl alcohol and varying amounts of citric acid adjusted to pH 3.7 at t=0, 20, 60 and 90 minutes. Samples of blood were taken prior to the administration of rsCT at these time points as well as at t=120 and 150 minutes. The resulting plasma samples were analyzed for rsCT by radioimmunoassay. Maximum rsCT levels were detected at t=120 minutes. The results of this study as shown in Table 1 indicate that the bioavailability and peak concentration of rsCT was a function of the concentration of citric acid in the formulation.

Paragraph at page 14, lines 12-24:

Example 2

The following study examines the effect of different preservatives on the plasma concentration of nasally administered salmon calcitonin. Rats were administered intranasally as



described previously 20µl of sCT (200µg/ml) in 0.85% sodium chloride, 0.1% [Tween] TWEEN[®] 80 and a combination preservatives of either 0.2% phenylethyl alcohol and 0.5% benzyl alcohol or 0.27% methyl parabens and 0.04% propyl parabens at t=0, 30, 60 and 90 minutes. The results of this study as shown in Table 2 indicate that the bioavailability and peak concentration of rsCT are not significantly affected by the addition of the different preservatives.

Paragraph at page 15, line 11 to page 16, line 6:

Example 3

The following study examines the effect of the concentration of citric acid on the stability of salmon calcitonin stored for varying periods at a temperature of 50°C. Nasal formulations containing sCT (200µg/ml), 0.25% phenylethyl alcohol, 0.5% benzyl alcohol and 0.1% [Tween] TWEEN[®] 80 were adjusted to pH 3.7 with either HCl or the indicated amount of buffered citric acid. The formulations were stored at 50°C in sealed glass containers for the indicated amount of time and analyzed for sCT by high performance liquid chromatography. The results as shown in Table 3 indicate that in the absence of citric acid, the amount sCT in the formulation decreased steadily between 0 and 9 days after the study was begun. In the presence of citric acid (10-50 mM) the rate of disappearance of sCT decreased significantly. However, as the concentration of citric acid was further increased, the rate of sCT disappearance from vials stored at 50°C increased in proportion to the amount of buffered citric acid in the formulation.

CLAIMS:

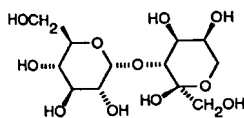
16. The liquid pharmaceutical composition of claim 1 further containing at least 0.1% by weight of [Tween 80] polyoxyethylene(20) sorbitan monooleate.

18. A liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 10 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween 80] polyoxyethylene(20) sorbitan monooleate.

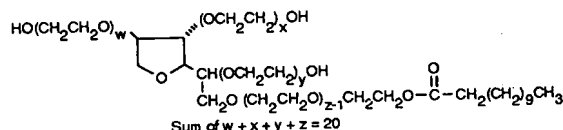
19. A liquid pharmaceutical composition comprising about 2,200 MIC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% [Tween 80] polyoxyethylene(20) sorbitan monooleate.

4% [7440-33-7] W FW 183.85	10g	38.10
RECS# Y07175000 FLAMMABLE SOLID	100g	249.60
5% [7440-33-7] W	10g	21.10
	50g	69.90
3-1.0 micron, 99.9+% [7440-33-7] W	100g	14.30
	500g	47.80
99.9+%, in hexanes [7440-33-7] W	5g	25.30
Merck Index 12,9945 FLAMMABLE LIQUID		
100 nm diameter powder which may structure and internal energy		
[7440-33-7] W	100g	26.60
	500g	94.50
[7440-33-7] W FW 183.85	24g	63.15
S 1(3),3227J RECS# Y07175000		
[7440-33-7] W	15g	34.10
[7440-33-7] W	18.9g	46.00
	94.5g	170.90
6 [7440-33-7] W	9.5g	28.40
	95g	179.05
1 solution d 1.010 Fp none Safety 2,3558A	100mL	16.60
Exact W concentration on label		
1 solution d 1.010 Fp none Safety 2,3558B	100mL	16.60
Exact W concentration on label		
d 1.012 Fp none	100mL	45.70
W concentration on label		
9-10		
007-09-9] WB FW 194.66 R&S 1(3),3265H	25g	28.20
FW 583.40 CORROSIVE	1g	14.70
	5g	48.30
99% [12070-12-1] WC FW 195.86	100g	29.70
Y07250000	500g	116.30
8] (tungsten tetrachloride) WCl ₄	5g	47.50
D CORROSIVE MOISTURE-SENSITIVE	25g	158.00
01-7] WCl ₆ FW 396.57 mp 275° bp 347°	10g	48.70
R&S 1(3),3335E RECS# Y07710000	100g	208.10
6	100g	71.40
	6x100g	318.10
13520-76-8] WO ₂ Cl ₂ FW 286.76	1g	17.20
	10g	95.00
6] (tungsten hexafluoride) WF ₆	225g†	298.60
12,9946 RECS# Y07720000	450g†	453.70
+% [14040-11-0] W(CO) ₆ FW 351.91	5g	85.20
	25g	284.00
-0] W(CO) ₆	10g	36.40
	50g	130.00
22-5] WO ₂ FW 215.85 IRRITANT	10g	25.50
	50g	81.60
1] WO ₃ FW 231.85 d 7.160	10g	48.00
(3),3283K RECS# Y07760000 IRRITANT	50g	149.30
	250g	578.20
, 99+% [1314-35-8] WO ₃	100g	32.10
	500g	105.60
	2kg	288.30
8-0] WOCl ₄ FW 341.66 mp 211°	5g	59.50
SENSITIVE IRRITANT	25g	205.30

Tungsten s		
39,944-2	Tungsten silicide, -325 mesh [12039-88-2] WSi ₂ FW 240.02	10g 16.1
		50g 32.1
24,363-9	Tungsten(IV) sulfide, powder, <2 micron, 99% [12138-09-9] WS ₂ FW 247.98	50g 30.1
	d 7.500 Safety 2,3559B R&S 1(3),3299E IRRITANT	
	Tungsten tetrachloride, see 26,397-4, Tungsten(IV) chloride page 1712	
45,906-2	Tungstic acid, 99.999% [7783-03-1] H ₂ WO ₄ FW 249.86 d 5.500	5g 33.1
	Merck Index 12,9948 FT-IR 1(2),1246C RECS# Y07840000 IRRITANT	25g 109.1
22,332-8	Tungstic acid, 99% [7783-03-1] H ₂ WO ₄	5g 16.1
		100g 29.1
		500g 114.1
	Tuppy's maleimide, see D14,080-5, N-(4-Dimethylamino-3,5-dinitrophenyl)maleimide page 637	
28,737-7	D-Turanose, 98% [547-25-1] (3-O-α-D-glucopyranosyl-D-fructose) FW 342.30	1g 24.1
	mp 170°(dec.) [α] _D ²⁰ +75° (c=4, H ₂ O) Beil. 31,454 Merck Index 12,9951	5g 99.1
	FT-NMR 1(1),308C R&S 1(1),197F	
	Turquoise Blue, see 30,647-9, Reactive Blue 15 page 1460	
27,434-8	Tween® 20 [9005-64-5] [polyoxyethylene(20) sorbitan monolaurate] n _D ²⁰ 1.4680	25mL 11.1
	d 1.095 Fp >230°F(110°C) R&S 1(1),761E RECS# TR7400000	500mL 17.1
	Average M _n ca. 1,228. HLB 16.7	4L 57.1
		18L 199.1
27,435-6	Tween® 40 [9005-66-7] [polyoxyethylene(20) sorbitan monopalmitate] n _D ²⁰ 1.4700	25mL 12.1
	d 1.083 Fp >230°F(110°C) R&S 1(1),761F RECS# WG2933000	500mL 17.1
	Average M _n ca. 1,284. HLB 15.6	4L 58.1
37,425-3	Tween® 60 [9005-67-8] [polyoxyethylene(20) sorbitan monostearate] d 1.044	25mL 11.1
	Fp >230°F(110°C) R&S 1(1),761G RECS# WG2934000	500mL 17.1
	Average M _n ca. 1,312. HLB 14.9	4L 57.1
27,436-4	Tween® 80 [9005-65-6] [polyoxyethylene(20) sorbitan monooleate] n _D ²⁰ 1.4720	25mL 11.1
	d 1.064 Fp >230°F(110°C) Merck Index 12,7742 R&S 1(1),761H RECS# WG2932500	500mL 17.1
	IRRITANT	4L 57.1
	Average M _n ca. 1,310. HLB 15.0	18L 19.1
38,890-4	Tween® 85 [9005-70-3] [polyoxyethylene(20) sorbitan trioleate] n _D ²⁰ 1.4680	25mL 11.1
	d 1.028 Fp >230°F(110°C) R&S 1(1),761I RECS# WG2934500	500mL 17.1
	Average M _n ca. 1,839. HLB 11.0	4L 57.1
21,679-8	Twort Stain λ _{max} 634(539)nm FT-IR 1(2),1043C Safety 2,3561B R&S 1(2),2843F	10g 3.1
	UV-Vis 723 CANCER SUSPECT AGENT	
	A 1 to 1 complex of Light Green SF and Neutral Red used as a stain for microorganisms in tissues and in the staining of bacteria, yeasts and algae under various conditions.	
T9,034-4	Tyramine, 99% [51-67-2] [4-(2-aminoethyl)phenol] HOC ₆ H ₄ CH ₂ CH ₂ NH ₂	5g 1.1
	FW 137.18 mp 161-163° bp 175-181°/8mm Beil. 13,625 Merck Index 12,9966	25g 6.1
	FT-NMR 1(2),612A FT-IR 1(1),1289C Safety 2,3562A R&S 1(1),1489I	
	RECS# SJ5950000 IRRITANT	
T9,035-2	Tyramine hydrochloride, 98% [60-19-5] [4-(2-aminoethyl)phenol hydrochloride]	5g 1.1
	HOC ₆ H ₄ CH ₂ CH ₂ NH ₂ ·HCl FW 173.65 mp 271-274° Beil. 13,625 Merck Index 12,9966	25g 6.1
	FT-NMR 1(2),612B FT-IR 1(1),1289D Safety 2,3562B R&S 1(1),1489J	
	RECS# SJ6050000 IRRITANT	
T9,039-5	DL-m-Tyrosine, 99% [775-06-4] [3-(3-hydroxyphenyl)-DL-alanine]	1g 1.1
	HOC ₆ H ₄ CH ₂ CH(NH ₂)CO ₂ H FW 181.19 mp 280-285°(dec.) Beil. 14,605	5g 1.1
	FT-NMR 1(2),1187A FT-IR 1(2),254D R&S 1(2),1845I RECS# YP2278000 IRRITANT	
85,545-6	D-Tyrosine, 99% [556-02-5] [(R)-(+)-tyrosine, 3-(4-hydroxyphenyl)-D-alanine]	500mg 1.1
	4-(HO)C ₆ H ₄ CH ₂ CH(NH ₂)CO ₂ H FW 181.19 mp >300° [α] _D ²⁰ +10.3° (c=4, 1N HCl)	1g 1.1
	Beil. 14,605 FT-NMR 1(2),1188A FT-IR 1(2),255C Safety 2,3565A R&S 1(2),1845M	5g 1.1
	IRRITANT	
	99% ee/GLC	
48,890-9	DL-Tyrosine-β- ¹³ C, 98 atom % ¹³ C [93627-94-2] 4-(HO)C ₆ H ₄ ¹³ CH ₂ CH(NH ₂)CO ₂ H	250mg 4.1
	FW 182.19 mp 325°(dec.) IRRITANT	
	Manufactured by ISOTEC INC.	
49,232-9	DL-Tyrosine- ¹⁵ N, 99 atom % ¹⁵ N [35693-13-1] 4-(HO)C ₆ H ₄ CH ₂ CH(¹⁵ NH ₂)CO ₂ H	500mg 2.1
	FW 182.19 mp 235°(dec.) IRRITANT	
	Manufactured by ISOTEC INC.	



28,737-7



27,434-8